REMARKS/ARGUMENTS

In view of the amendments above and the remarks and arguments below, Applicant believes the pending application is in condition for allowance.

I. Status of the Claims

Claims 1-8 were previously pending.

Claims 2-8 are amended as follows. Claim 1 is not amended.

Claims 2 and 3 are amended to clarify the definitions of the variables R1, R2, R3, R4, and n. Support for the amendments can be found in the Specification of record,[1] for example, on page 12, line 19 through page 14, line 7. No new matter is introduced by the amendments.

Claim 2 is further amended to clarify that in step 2, a reducing agent is used to hydrogenate the compound represented by formula (3). Support for the amendment can be found in the Specification of record, for example, on page 16, lines 1-16. No new matter is introduced by the amendment.

Claims 4-8 are amended to recite method claims instead of product claims. Support for the amendments can be found, for example, in the original product claims and in the Specification of record on page 20, line 19 through page 21, line 10 and on page 24, line 23 through page 25, line 18. No new matter is introduced by the amendments.

Claims 1-8 are currently pending and at issue.

II. Rejection of Claims 2-8 under 35 U.S.C. § 112, ¶ 2

Claims 2-8 are rejected under 35 U.S.C. § 112, ¶ 2, as indefinite. Specifically, the Examiner states that:

[1] Applicant respectfully submits that the Specification currently of record is the clean copy of a substitute specification that was filed with a Second Preliminary Amendment on January 4, 2006.

- in claims 2 and 3, the expression "wherein, R1, R2, R3, R4 and n are the same as previously defined" is vague and indefinite because each of the variables R1, R2, R3, R4 and n is undefined within the claims; and
- in claim 2, the expression "the resulting compound is converted to an amino group using a reducing agent" is vague and indefinite because the claim does not specify how or what kind of a resulting compound is converted to an amino group.

Applicant appreciatively thanks Examiner Oh for pointing out these informalities.

In response, Applicant has amended the claims so that:

- in claims 2 and 3, the variables R1, R2, R3, R4, and n are defined within the claims; and
- in claim 2, it is clear that it is on the compound represented by formula (3) that a hydrogenation reaction is conducted.

Accordingly, Applicant respectfully submits that claims 2-8 are no longer indefinite, and respectfully requests that the rejection of claims 2-8 under 35 U.S.C. § 112, ¶ 2, be withdrawn.

III. Rejection of Claims 1-8 under 35 U.S.C. § 103(a)

Claims 1-8 are rejected under 35 U.S.C. § 103(a) as unpatentable over a journal article authored by Ohkawa et al.[2] ("Ohkawa") in view of European Patent Application Publication No. 0 483 772 A1 by Aono et al. ("Aono"). The Examiner contends that Ohkawa in combination with Aono renders the claims obvious.

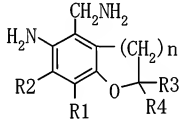
Applicant respectfully traverses the rejection. Specifically, Applicant respectfully submits that the Examiner's case of *prima facie* obviousness is rebutted by evidence of superior, unexpected results achieved by the present invention discussed below. "A *prima facie* case of obviousness

[2] S. Ohkawa et al., "5-Aminocoumarans: Dual Inhibitors of Lipid Peroxidation and Dopamine Release with Protective Effects against Central Nervous System Trauma and Ischemia", *Journal of Med. Chem.*, **40**, 559-573 (1997).

based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior results."[3]

The present invention aims to treat cerebrovascular disorder, circulatory disorder, cerebral infarction, or retinal oxidation disorder, or to inhibit retina disorder of age-related macular degeneration or diabetic retinopathy. Accordingly, an antioxidant to be administered for such purposes is required to cross the blood-brain barrier into the central nervous system.

The antioxidant according to the present invention is represented by the following formula (1):

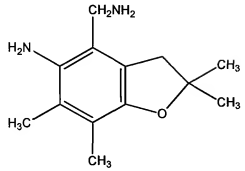


(1)

wherein R1, R2, R3 and R4 respectively and independently represent a hydrogen atom or a C_{1-6} alkyl group, and n represents an integer of 1 or 2.

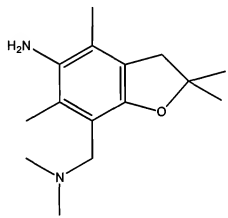
For example, the present specification has demonstrated in Examples 4 to 6 that Compound 1 represented by the following formula:

[3] MPEP § 2144.09, subsection VII, first sentence.



exhibits high antioxidative action and crosses the blood-brain barrier into the central nervous system.

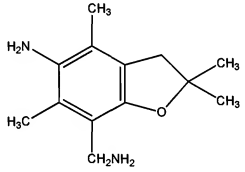
In contrast, Ohkawa and Aono disclose 5-aminocoumarans developed for the treatment of traumatic and ischemic central nervous system injury, and exemplify "Compound 19a" represented by the following formula.



As shown in Table 2 of Ohkawa, the percent inhibition of lipid peroxide formation in rat liver microsomes by 1 μM of Compound 19a was 4%, and the dose of Compound 19a (administered orally) required to reduce by 50% the score of excitatory behavior induced by intrathecal injection

of $FeCl_2$ (ID_{50}) was more than 50 mg/kg. Thus, the antioxidative action of Compound 19a is not sufficient not only *in vivo* but also *in vitro*.

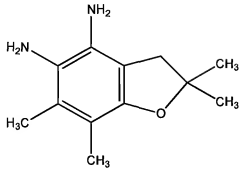
In addition, Applicant synthesized Compound A represented by the following formula and conducted evaluations in terms of antioxidative action *in vitro* and tissue migration as shown in the Declaration under 37 CFR § 1.132 submitted with this Response.



As a result, the molar concentration of Compound A required to reduce the amount of brain peroxide formed *in vitro* by 50% was more than 10 μM and the percent inhibition of brain peroxide-formation *ex vivo* by Compound A was 8%. Thus, the migration into the brain of Compound A is not sufficient and the antioxidative action thereof *in vitro* is also not sufficient.

Since neither Compound 19a nor Compound A exhibits sufficient antioxidative action as described above, Applicant respectfully submits that it would not be obvious for those skilled in the art to arrive at the antioxidant represented by the formula (1) by changing the position of a substituent of Compound 19a or Compound A.

In addition, Ohkawa and Aono disclose "Compound 11" represented by the following formula.



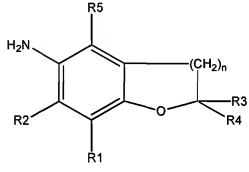
As shown in Table 2 of Ohkawa, the molar concentration of Compound 11 required to reduce the amount of lipid peroxide formed in rat liver microsomes by 50% (IC_{50}) was 0.30 μM and ID_{50} of Compound 11 was more than 50 mg/kg. Thus, Compound 11 does not exhibit antioxidative action *in vivo*, although Compound 11 exhibits antioxidative action *in vitro*.

In the same manner, the antioxidative action *in vitro* and *in vivo* of Compound 11 was evaluated as "Control Drug 1" in Examples 4 and 6 of the present specification. The results showed that Compound 11 does not exhibit antioxidative action *in vivo*, although Compound 11 exhibits antioxidative action *in vitro* at the same level as that of Compound 1. Thus, it is apparent that Compound 11 cannot easily cross the blood-brain barrier into the central nervous system, and therefore Compound 11 cannot exhibit sufficient antioxidative action *in vivo* at a small dose.

In contrast, Compound 1 exhibited excellent antioxidative action not only in *vitro* but also *in vivo*. That is, it has been demonstrated that Compound 1 can easily cross the blood-brain barrier into the central nervous system, and therefore it can exhibit excellent antioxidative action *in vivo* even at a small dose.

Moreover, Applicant respectfully submits that the Declaration under 37 CFR § 1.132 submitted herewith further demonstrates that Compound 1 exhibits significantly superior antioxidative action on the retina to that of Compound 11. As shown in the Declaration, Compound 1 migrated into the retina to exhibit excellent antioxidative action thereon, while Compound 11 neither migrated into the retina nor exhibited antioxidative action.

As described above, the properties of Compound 1 are quite different from those of the compounds disclosed in Ohkawa or Aono. For this, Applicant believes that a methylamino group as R5 in the following formula (A):



(A)

plays an important role to allow a compound to cross the blood-brain barrier into the central nervous system to exhibit antioxidative action in *vivo*. Since neither Ohkawa nor Aono teaches that R5 has to be a methylamino group for this purpose, Applicant respectfully submits that it would not have been obvious at the time of the present invention for those skilled in the art to arrive at the compound represented by the formula (1) based on Ohkawa and Aono, either alone or in combination.

Accordingly, Applicant respectfully submits that the *prima facie* case of obviousness presented by the Examiner is rebutted, and that pending claims 1-8 are patentable over Ohkawa in view of Aono. Thus, Applicant respectfully requests that the rejection of claims 1-8 be withdrawn.

CONCLUSION

In view of the foregoing, it is believed that claims 1-8 are in immediate condition for allowance and it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: September 2, 2008

Respectfully submitted,

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